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EXAMINER	
KLINKEL, KORTNEY L	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,318	GAMELIN ET AL.	
	Examiner	Art Unit	
	Kortney L. Klinkel	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6 and 11-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6 and 11-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Acknowledgement is made of the remarks/amendments filed 12/28/2009. Claims 1, 4-6 and 11-14 have been amended. Claims 2-3 and 7-10 stand canceled. Claims 1, 4-6 and 11-14 are pending in the instant Office action.

Claim Rejections - 35 USC § 112 2nd Paragraph—Withdrawn

The rejection of claims 1, 4-5, 12 and 14 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 102—Withdrawn

The rejection of claims 1, and 4 under 35 U.S.C. 102(b) as being anticipated by Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts," Therapie, 53, 183, 1998, as per Applicant's IDS) is withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 103—Withdrawn

The rejection of claims 5-6 and 11-12 under 35 U.S.C. 103(a) as being unpatentable over Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts," Therapie, 53, 183, 1998) is withdrawn in light of the claim amendments.

The rejection of claims 13-14 under 35 U.S.C. 103(a) as being unpatentable over Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts," Therapie, 53, 183, 1998), in view of Chazard (US Patent Publication US 2002/0045632) is withdrawn in light of the claim amendments.

Claim Rejections - 35 USC § 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6, 11, and 13-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection which was originally presented in the Office action dated 8/27/2009, is maintained. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 6 and 13 have been amended to recite at least 1 g calcium and at least 1 g of magnesium and at least 1 g/day. There is no support in the instant specification for these limitations. The specification provides support for 1 g calcium and 1 g magnesium (see [0030]) and 1 g/day (see [0031]), but not for any amounts greater or less than these amounts.

Response to Arguments

Applicant's arguments submitted 12/28/2009 regarding the rejected claims for new matter has been fully considered, but is not persuasive. Applicant argues that the specification provides support for the recited "at least 1 g" of calcium and magnesium and "at least 1 g/day" and points to paragraphs 24 and 25 for support. This argument is not persuasive. The phrase "at least 1 g" includes any amount just larger than 1 g up to an infinite number of grams. Paragraphs 24 and 25 of the instant specification provide support for amounts of calcium and magnesium administered per day which are larger than 1 g, but these paragraphs do not provide support for the full range of dosage amounts encompassed by the phrase "at least 1 g". Based off the disclosure of paragraphs 24 and 25, applicant is entitled to amounts of calcium and magnesium together of 2-3 g/day I.V. or 1-2 g/day oral calcium. The instant specification fails to provide written support for the claimed amounts of "at least 1 g" and "at least 1 g/day" with respect to calcium and magnesium.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts," Therapie, 53, 183, 1998), in view of Chazard (US Patent Publication US 2002/0045632).

Laine-Cessac et al. teaches that the anticancer agent oxaliplatin induces neurotoxicity (1st sentence). This neurotoxicity can be dramatically improved by treating patients undergoing oxaliplatin treatment with intravenous calcium gluconate (1g) and magnesium sulfate (1g). Laine-Cessac et al. also teach that the exact mechanism of oxaliplatin neurotoxicity is unknown, but that it is thought to be linked to either hypomagnesaemia or hypocalcaemia or both. A related platinum containing cancer treatment drug, cisplatinum is known to produce renal magnesium wasting resulting in

hypomagnesaemia, hypocalcaemia and hypokalaemia. It is also hypothesized that the oxaliplatin toxicity stems from the drug or its metabolites chelating calcium (2+) or magnesium (2+) cations.

Laine-Cessac et al. teaches a combination useful for sequential administration in anticancer therapy comprising oxaliplatin, injectable calcium, injectable magnesium as well as calcium in the oral form. Please note that there is nothing present in the injectable calcium formulation taught by Laine-Cessac et al. that would prevent one from taking it orally.

The teachings of Laine-Cessac et al. differ from the instant invention in that the injectable calcium and calcium in the oral form are not taught to be separate compositions.

Chazard teaches the use of an oral formulation of calcium folinate to potentiate the coadministration of oxaliplatin in order to treat tumors (abstract, paragraph 36). Chazard teaches the calcium folinate is to be administered for 1-14 days ([0036]) at a dosage of 90 mg/day (see [0035]). More generically Chazard teaches that calcium folinate can be administered in an amount of 0.1 to 500 mg/kg/day ([0018]). Chazard also teaches an example (Example 2, [0033]-[0041]) calculating the maximal tolerated dose of oxaliplatin with calcium folinate ([0033]). Chazard teaches that 19 subjects ([0038]) were treated with up to 130 mg/m^2 of oxaliplatin while being treated with 90 mg/day of calcium folinate ([0035]) without experiencing dose limiting toxicity ([0038]). See the results of the decreased neurotoxicity in the table at paragraph [0040]. Note

particularly the occurances of parasthesia, and asthenia, two neurotoxic effects known to be attributed to oxaliplatin administration.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to assemble a kit containing oxaliplatin, injectable calcium, injectable magnesium and calcium in the oral form where the two calcium compositions are separate compositions with the reasonable expectation that this kit would be useful for decreasing the occurrence and/or severity of the neurotoxic effects of oxaliplatin. One would have been motivated to do so because it is well known in the art that Ca and Mg injections help to ameliorate the neurotoxic effects of oxaliplatin and oral Ca is also known to ameliorate the neurotoxic effects of oxaliplatin. "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 1, 4-6 and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laine-Cessac et al. ("Acute Oxaliplatin Neurotoxicity Dramatically Improved with Intravenous Calcium and Magnesium Salts," Therapie, 53, 183, 1998) in view of Grolleau et al. ("A possible explanation for a neurotoxic effect of the anticancer agent oxaliplatin on neuronal voltage-gated sodium channels, Journal of

Neurophysiology, 2001, 85, 2293-2297, as per Applicant's IDS) and Mazer et al. (US 5698222)

The teachings of Laine-Cessac et al. are set forth above. Laine-Cessac et al. fail to teach wherein the injectable and oral calcium are separate compositions as required by claim 1, and Laine-Cessac et al. do not teach the administration of oral calcium following the treatment with oxaliplatin as required by claims 6, 11 and 13-14.

Grolleau et al. teach that the administration of Ca and Mg ions act to prevent acute neurotoxic side effects of oxaliplatin treatment (abstract). Grolleau et al. cites Laine-Cessac et al. (applied above) and says that also, neurological effects induced by oxaliplatin can be strongly attenuated by pre- and post-treatment with Ca and Mg ion infusions. Grolleau et al. also discovered that one of the metabolites of oxaliplatin, oxalate, is responsible for complexing calcium ions which leads to the neurological effects of administering oxaliplatin (p. 2294 first column before Methods section, also Results section and p. 2297 first column). Grolleau et al. teach that when Ca and Mg are infused to patients before and after oxaliplatin administration, oxaliplatin-induced acute neurotoxicity was highly reduced becoming lower than 10% of grade 2 and 3 in 40 patients (p. 2297, concluding paragraph).

Mazer et al. teach that calcium is an essential nutrient (col. 1, line 10). The calcium balance in humans is influenced by several factors. Older age and oxalic acid act to inhibit calcium absorption (col. 1 lines 30-42, also Table 2 cols. 3-4). Table 1 also shows the optimal daily calcium intake for men and women. This daily dose ranges from 1.0 to 1.5 g/day. Sources of oral calcium include food (col. 1, lines 61-66), as well

as calcium supplements including calcium gluconate and calcium carbonate (col. 3, lines 14-17, col. 5, lines 20-27). These same sections also teach that calcium carbonate is usually recommended as an oral supplement because it contains more calcium per gram than any of the other calcium salts.

Regarding claims 1, 4-5 and 12 directed to a kit, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to assemble a kit containing oxaliplatin, injectable calcium, injectable magnesium and calcium in oral form where the two calcium compositions are separate compositions with the reasonable expectation that this kit would be useful for decreasing the occurrence and/or severity of the neurotoxic effects of oxaliplatin. Likewise regarding claims 6, 11, and 13-14, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to administer at least 1 g of injectable magnesium and at least 1 g of injectable calcium prior to and after administration of oxaliplatin as well as administer oral calcium after administration of oxaliplatin with the reasonable expectation that neurotoxicity caused by the administration of oxaliplatin would be inhibited or treated. One would have been motivated to do so because it is well known in the art that Ca and Mg injections both before and after oxaliplatin administration help to ameliorate the neurotoxic effects of oxaliplatin. One would have been particularly motivated to add an oral calcium form (i.e. either calcium gluconate or carbonate) to the kit and administer it because Mazer et al. teach that calcium is an essential nutrient and that men and women should consume from 1.0-1.5g/day. Mazer et al. also teaches that oxalic acid and older age (older than 51) deplete calcium absorption. The patients studied by

Laine-Cessac are all of older age (ages 49-73) and as taught by Grolleau, oxalate (the anion of oxalic acid) is a metabolite of oxaliplatin which acts to complex calcium and magnesium ions. Accordingly, the patients studied by Laine-Cessac et al. are all at particular risk, due both to older age and the presence of oxalic acid, of being low on calcium so one would be particularly motivated to supplement their diets with an oral form of calcium. Regarding the claimed amounts of at least 1 g with respect to the injectable calcium and magnesium, Laine-Cessac et al. teach the administration of 1 g of each of these. However, given the teachings of Grolleau et al. which show that both calcium and magnesium ions are depleted by the administration of oxaliplatin and that the administration of calcium and magnesium ions help inhibit the neurotoxicity caused by oxaliplatin, and given the fact that Mazer et al. teach that the recommended daily dose of calcium is from 1.0-1.5 g/d for healthy adults, one would be motivated to administer more than 1 g of injectable calcium and magnesium in order to assure that the subject being treated did not experience neurotoxicity. It would be nothing more than routine experimentation to come up with the optimal dosage amount. Regarding the dosage schedule set forth in claim 14, it would have been obvious to orally administer the calcium for 8 days after treatment because Mazer et al. teach that from 1.0-1.5 g/day calcium is recommended daily.

Regarding the concentrations of the injectable calcium and magnesium recited in claims 5 and 12, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to arrive at the claimed concentration between 8 and 20 mg/ml calcium ion and between 10 and 20 mg/ml magnesium ion, or more specifically 15

mg/ml magnesium ion, with a reasonable expectation of success based on the teachings of the prior art One would have been motivated to do so because Laine-Cessac et al. teach the administration of 1g total of both magnesium sulfate and calcium gluconate via IV. The IV implies that the calcium and magnesium ions must be in solution and in order to achieve this amount and meet the claimed concentrations, one would merely need to select an IV volume of roughly 150 ml which is a completely reasonable and typical IV volume to inject, especially given the fact that both calcium gluconate and magnesium sulfate are highly soluble in water as is well known in the art. Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, no more than routine experimentation would have been necessary to one of ordinary skill in the art to arrive at the claimed concentrations given that the total amount administered is taught by the prior art.

Response to Arguments

Applicant's arguments regarding the rejected claims have been fully considered but are moot in light of the new grounds of rejection necessitated by amendment.

Conclusion

Claims 1, 4-6, and 11-14 are rejected. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kortney Klinkel, whose telephone number is (571)270-5239. The examiner can normally be reached on Monday-Friday 10 am to 7 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at (571)272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

KLK

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